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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,404	02/13/2004	Roger K. Sunahara	UM-08794	7762

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EXAMINER	
GEBREYESUS, KAGNEW H	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,404	SUNAHARA ET AL.	
	Examiner	Art Unit	
	Kagnew H Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Priority from provisional application 60/447,074 filed on 02/13/2003 has been acknowledged.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10 and 19 are rejected under 35 U.S.C. 101 because the claimed inventions lack patentable utility. Claims 10 and 19 are rejected under 35 U.S.C. 101 because the claimed inventions are not supported by either a credible, specific and substantial asserted utility or a well established utility. Claim 10 is directed to a method that comprises admixing a nucleotide cyclase mutant (VC1-ACGC), a fluorescently labeled substrate, one or more test compounds, and determining the level of fluorescence of said fluorescently labeled substrate. Claim 19 is directed to a kit containing the nucleotide cyclase mutant (VC1-ACGC). Applicants in the example section of the specification, show the effect of forkolin on two distinct forms of mutant type II adenylyl cyclases: (VC1-ACGC) and VC1- (D396A) ACGC) and measure the resulting increase in fluorescence. Higher level of fluorescence was observed when VC1-ACGC was stimulated by forskolin as compared to for VC1- (D396A) ACGC. Although this assay shows the effect of a test compound on VC1-ACGC as compared to the effect on VC1- (D396A) ACGC), it is not clear how these results could be extrapolated to normal physiological conditions. It is not clear how this invention would be relevant to a physiological condition. In addition Gilles et al. disclose MANT-substituted guanine nucleotides that inhibit adenylate cyclases. In addition

Kawabe et al., 1996 have shown that GTP inhibits soluble adenylyl cyclase from Sf9 cells non-competitively. It is therefore unclear how a method of detecting the activity of such a mutant nucleotide cyclase is relevant or has any utility if the physiological substrate of the specific cyclase is changed since the resulting downstream signaling pathway would not reflect a normal physiological condition. The skilled artisan would not know how to use such a mutant given that the substrate specificity of the particular adenylyl cyclase (VC1-ACGC) has changed from ATP to GTP. The specification does not support the claim 10 and 19 with either a credible, specific and substantial or a well-established utility.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants enumerate method steps without clearly pointing out and stating what the claimed method is drawn to. Applicants need to clearly and distinctly claim the subject matter of the invention. For example "a method of detecting nucleotide cyclase enzyme activity comprising".....etc or "A method of identifying a compound that modulates nucleotide cyclase activity wherein".....etc.

3. Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 12-14 are rejected for the recitation of "suspected ligand" or "suspected

activator" or "suspected inhibitor". It is not certain what applicants intend or what qualities they refer by the recitation "suspected". How does one suspect a ligand or an activator or an inhibitor?

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 4-15 are rejected under 35 U.S.C. 112, first paragraph, based on a disclosure which is not enabling. Claim 1 is incomplete without a control reaction (a reaction without the test compound) since it is critical or essential to the practice of the invention, but not included in the claim(s) therefore is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). When examining the level of activity of any enzyme challenged with a test compound(s) one needs to also determine the level of enzyme activity in the absence of the test compound, thus the difference between the activity of the enzyme in the presence and absence of the test compound would reflect the net effect of the test compound on the activity of the enzyme. Claim 1 and dependent claims 4-15 are incomplete and are therefor not enabled.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5, 6 and 14 rejected under 35 U.S.C. 102(a) as being anticipated by Gille et al. Gille et. al. teach a fluorescently labeled GTP analog that are potent adenylyl cyclase inhibitors. Gille et. al. disclose a method of assaying adelylyl cyclase (AC) activity in the presence of 5mM $MgCl_2$ or in the presence of 10mM $MnCl_2$ and 100mm forskolin (an activator of AC activity) and a fluorescent GTP analog MANT-GTPγS thus Gille et. al.'s method encompasses the method steps disclosed by applicants, therefore anticipates claims 1, 5, 6 and 14.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1- 9, 11-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Dieter et. al. (US PAT 6323186 B1). Dieter et. al. disclose a method of fluorescent assay including protein binding assays and hydrolase enzymes which include nucleotide cyclases. A method of analyzing enzyme activity in a sample containing fluorescent GTP derivatives that encompasses BODIPY-FL-GTPγS as a substrate is disclosed, thus anticipating claims 1- 9, 12, 13, 15. Furthermore, a kit containing said substrate, an enzyme that hydrolyses the substrate inhibitors (claim 14) and a high throughput screening method, including microwell plates or microfluidic chips (anticipating claim 11, 16-18 and 20) are disclosed. Therefore, Dieter et. al. anticipate the claimed inventions in claims 1- 9, 11-18 and 20.

9. Claims 1-3, 5, 9, 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Rossomando et. al. (Proc. Natl. Acad. Sci. USA Vol 78, No. 4 pp. 22782282, 1981).

Rossomando et. al disclose the use of formycin 5'-triphosphate, a non-radioactive fluorescent analog of ATP, as a substrate to assay the activity of the membrane bound form of adenylate cyclase from rat osteosarcoma cells in an in-vitro assay. In the detailed experimental procedures reaction mixtures to carry out the non-radioactive fluorescent assay include the fluorescent substrate, membrane protein containing the membrane bound form of adenylyl cyclase to detect its activity thus anticipating claims 1-3, 5, 9, and 12-15.

10.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1- 9 and 11-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et al. (US 2002/0064849 A1) in view of Gille et. al. ("MANT-substituted guanine nucleotides: A

novel class of potent adenylyl cyclase inhibitors", Life Sciences 74, 271-279 (2003) or McEwen et. al.

Herr et al. teach a method of measuring adenylyl cyclase activity in a sample containing a human soluble adenylyl cyclase and a compound that can potentially affect the activity of the adenylyl cyclase by measuring the amount of cAMP formed from ATP. However Herr et al. measure the level of cAMP produced using radioimmunoassay. Gille et. al. teach the use of MANT-substituted guanine nucleotides such as MANT-GTPγS to study the kinetics of adenylyl cyclase/nucleotide interactions as well as function, trafficking and localization of adenylyl cyclase enzymes in intact cells. McEwen et. al teach the use of BODIPY- GTPγS to study the kinetics of receptor-mediated and ligand induced guanine nucleotide exchang in vitro. Given that it would be advantageous to use a non-radioactive assay from the standpoint of cost and environmental and personal safety, and time one would be motivated to substitute the fluorescent substrate disclosed in Gilles et. al. or the BODIPY- GTPγS of McEwen et. al. for the radioactively labled substrate of Herr et. al. to evaluate the effect of a test compound on the activity of adenylyl cyclase. In addition given that the hydrophobic pocket is conserved among membranous adenylyl cyclases and soluble gualylyl cyclases as disclosed by Gille et. al., one of ordinary skill in the art would have reasonable expectation of success to use MANT-GTPγS in kinetic studies of soluble guanylyl cyclases. Furthermore applicant's method of using a fluorescent nucleotide analog would be obvious in view of the kinetic studies performed by Gille et. al who established direct interaction and effect of a fluorescent nucleotide analogue (MANT-GTPγS) with adenylyl cyclase and one of ordinary skill in the art would be motivated to use the BODIPY- GTPγS substrate of McEwen to study the kinetics of any nucleotide cyclase with a reasonable expectation of success.

Claims 6, 7 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et al. (US 2002/0064849 A1) in view of Rossomando et.al. As stated above Herr et al. teach a method of assaying the activity of soluble adenylyl cyclase activity by measuring cAMP levels with a radioimmunoassay technique. Rossomando et. al. teach the use of Formycine A (a florescent ATP analog) to assay for adenylate cyclase activity comprising a reaction mixture containing membrane protein (which contains membrane bound adenylyl cyclase), formycine A (ATP analog) and measuring the level of fluorescence of the cyclic compound cFoMP (cAMP analog). It would have been obvious for a person skilled in the art to replace the membrane protein used by Rossomando et. al. to assay for the activity of any form of adenylyl cyclase (e.g. soluble adenylyl cyclase) in the reaction of Rossomando et al. with a reasonable expectation of success in quantifying fluorescence levels reflective of adenylyl cyclase activity. Furthermore it also would have been obvious to provide all components of the assay of Rossomando et al. together in a packaged system in order to provide added convenience to one utilizing the method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

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Kagnew Gebreyesus PhD.